PCT/EP2004/012082
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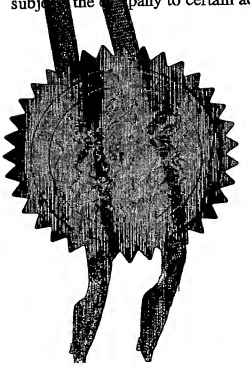

Signed Andrew Ganey

Dated 5 October 2004

PRIORITY DOCUMENT

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Patents Form 1/77

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1/77
29OCT03 E847657 D00245
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
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South Wales NP10 8QQ

1.	Your reference	4-33439P1
2.	Patent application number *(The Patent Office will fill in this part)*	27 OCT 2003 0325032.1
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7254870005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Bernard A. Marsh
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country / Priority application number *(if you know it)* / Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application / Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	13
Claim(s)	6
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Bernard A. Marsh 27th October 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. Trevor Drew 01403 323069

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Notes

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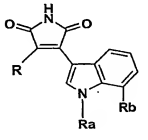
Organic Compounds

The invention relates to the use of compounds (hereinafter: "COMPOUND ") or a N-Oxide or a pharmaceutically acceptable salt thereof having an activity on protein kinases PKC alpha, PKC beta, PKC gamma, PKC epsilon, PKC theta, CDK-1, KDR, PKA, Flt-1, Flt-2, Flt-3 or Flt-4, or on a combination of the above enzymes, for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

COMPOUND is preferably a compound of formula I



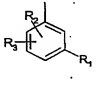
I

wherein

Ra is H; CH3; CH2-CH3; or isopropyl,

Rb is H; halogen; C1-6alkoxy; or C1-6alkyl, and either

I. R is a radical of formula (a)



(a)

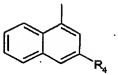
wherein

R1 is piperazin-1-yl optionally substituted by CH3 in position 3 or 4; or 4,7-diaza-spiro [2.5] oct-7-yl;

R2 is Cl; Br; CF3; or CH3; and

R3 is H; CH3; or CF3; R3 being other than H when Ra is H or CH3, Rb is H and R1 is 4-methyl-1-piperazinyl; or

II. R is a radical of formula (b)



(b)

wherein

R4 is piperazin-1-yl substituted in positions 3 and/or 4 by CH3; or 4,7-diaza-spiro [2.5] oct-7-yl; Ra being other than H or CH3 when R4 is 4-methyl-1-piperazinyl; or

III. R is a residue of formula (c)

(c)

wherein

R14 is piperazin-1-yl optionally substituted by CH3 in position 3 and/or 4 or in position 3 by ethyl, phenyl-C1-4alkyl, C1-4alkoxy-C1-4alkyl or halogeno–C1-4alkyl; or 4,7-diaza-spiro [2.5] oct-7-yl;

R15 is halogen; CF3; or CH3; R15 being other than CH3 when Ra is H or CH3, Rb is H and R14 is 4-methyl-1-piperazinyl; and

R16 is H; CH3; or CF3; R16 being other than H when R15 is Cl, Ra is H or CH3, Rb is H and R14 is 4-methyl-1-piperazinyl; or

IV. R is a radical of formula (d)

(d)

wherein R8 is piperazin-1-yl, 3-methyl-piperazin-1-yl or 4-benzyl-piperazin-1-yl; or

V. R is a radical of formula (e)

(e)

wherein R9 is 4,7-diaza-spiro [2.5] oct-7-yl; or piperazin-1-yl substituted in position 3 by methyl or ethyl and optionally in position 4 by methyl.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid, trifluoroacetic acid.

It will be appreciated that the compounds of formula I may exist in the form of optical isomers, racemates or diastereoisomers. For example, a ring carbon atom bearing a substituent in the position 3 of the piperazinyl residue is asymmetric and may have the D- or L- configuration. It is to be understood that the present invention embraces all enantiomers and their mixtures. Similar considerations apply in relation to starting materials exhibiting asymmetric carbon atoms as mentioned.

Or more preferably COMPOUND is a compound selected from any of the examples 1 to 88. The compounds of examples 1 to 88 are of formula I, as herein before described, wherein

In examples 1 to 19 R is of formula (a)

Example	R_1	R_2	R_3	R_a	R_b	M.S. Data
1	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	H	H	MH^+ 435
2	-(4-methyl-piperazin-1-yl)	2-CH_3	3-CH_3	CH_3	H	MH^+ 429
3	-(4-methyl-piperazin-1-yl)	2-CH_3	3-CH_3	H	H	MH^+ 415
4	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	CH_3	H	MH^+ 449
5	1-piperazinyl	2-Cl	3-CH_3	H	H	MH^+ 421
6	1-piperazinyl	2-Cl	3-CH_3	CH_3	H	MH^+ 435
7	3-*R*-methyl-piperazin-1-yl	2-Cl	3-CH_3	CH_3	H	MH^+ 449
8	3-*R*-methyl-piperazin-1-yl	2-Cl	3-CH_3	H	H	MH^+ 435
9	1-piperazinyl	2-Cl	3-CF_3	CH_3	H	MH^+ 503
10	1-piperazinyl	2-Cl	3-CF_3	H	H	MH^+ 489
11	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	H	$CH(CH_3)_2$	MH^+ 477
12	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	H	CH_3	MH^+ 449
13	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	H	CH_2-CH_3	MH^+ 463
14	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	H	Cl	MH^+ 469
15	-(4-methyl-piperazin-1-yl)	2-Cl	3-CH_3	H	F	MH^+ 453
16	-(4,7-diaza-spiro[2.5]oct-7-yl)	2-Cl	H	H	CH_2-CH_3	MH^+ 462
17	-(4,7-diaza-spiro[2.5]oct-7-yl)	2-Cl	H	H	Cl	MH^+ 468
18	-(4,7-diaza-spiro[2.5]oct-7-yl)	2-Cl	H	H	CH_3	MH^+ 447
19	-(4,7-diaza-spiro[2.5]oct-7-yl)	2-Cl	H	H	H	MH^+ 434

And,

In examples 20 to 28 R is of formula (b)

Example	R_4	R_a	M.S. Data
20	-(4,7-diaza-spiro[2.5]oct-7-yl)	CH_3	MH^+ 463

21	3-*R*-methyl-piperazin-1-yl	CH_3	MH^+ 452
22	-(4,7-diaza-spiro[2.5]oct-7-yl)	CH_3	MH^+ 464
23	-(4,7-diaza-spiro[2.5]oct-7-yl)	H	MH^+ 450
24	3-*R*-methyl-piperazin-1-yl	H	MH^+ 438
25	3-*S*-methyl-piperazin-1-yl	CH_3	MH^+ 452
26	3-*S*-methyl-piperazin-1-yl	H	MH^+ 438
27	4-methyl-3-*S*-methyl-piperazin-1-yl	CH_3	MH^+ 466
28	4-methyl-3-*S*-methyl-piperazin-1-yl	H	MH^+ 452

And

In examples 29 to 57 R is of formula (c)

Ex.	R_{14}	R_{15}	R_{16}	R_a	R_b	M.S. Data
29	-(4-methyl-piperazin-1-yl)	Cl	CH_3	H	H	MH^+ 437
30	-(4-methyl-piperazin-1-yl)	Br	H	H	H	MH^+ 469
31	-(4-methyl-piperazin-1-yl)	Br	CH_3	H	H	MH^+ 483
32	-(4-methyl-piperazin-1-yl)	Br	H	CH_3	H	MH^+ 483
33	-(4-methyl-piperazin-1-yl)	CF_3	H	H	H	MH^+ 457
34	-(4-methyl-piperazin-1-yl)	CF_3	H	CH_3	H	MH^+ 471
35	3-*R*-methyl-piperazin-1-yl	Cl	CH_3	H	H	MH^+ 437
36	-(4,7-diaza-spiro[2.5]oct-7-yl)	Cl	CH_3	H	H	MH^+ 449
37	1-piperazinyl	Cl	CH_3	H	H	MH^+ 423
38	4-methyl-3-*R*-methyl-piperazin-yl	Cl	CH_3	H	H	MH^+ 451
39	3-R-methoxyethyl-piperazin-1-yl	Cl	CH_3	H	H	MH^+ 481
40	3-R-ethyl-piperazin-1-yl	Cl	CH_3	H	H	MH^+ 451
41	3-R-benzyl-piperazin-1-yl	Cl	CH_3	H	H	MH^+ 514
42	3-S-methyl-piperazin-1-yl	Cl	CH_3	H	H	MH^+ 437
43	4-methyl-piperazin-1-yl	Cl	CH_3	H	CH_2-CH_2-CH_3	MH^+ 479
44	3-CH_2F-piperazin-1-yl	Cl	CH_3	H	H	MH^+ 453
45	4-methyl-piperazin-1-yl	Cl	CH_3	H	F	MH^+ 455
46	4-methyl-piperazin-1-yl	Cl	CH_3	H	$CH(CH_3)_2$	MH^+ 479
47	4-methyl-piperazin-1-yl	Cl	CH_3	H	Cl	MH^+ 471
48	4-methyl-piperazin-1-yl	Cl	CH_3	H	OCH_3	MH^+ 467
49	4-methyl-piperazin-1-yl	Cl	CH_3	H	CH_3	MH^+ 451

50	4-methyl-piperazin-1-yl	Cl	CH_3	H	CH_2-CH_3	MH^+ 465
51	4-methyl-piperazin-1-yl	CF_3	H	H	CH_2-CH_3	MH^+ 485
52	4-methyl-piperazin-1-yl	CF_3	H	H	CH_3	MH^+ 471
53	4-methyl-piperazin-1-yl	F	H	H	H	MH^+ 407
54	4-methyl-piperazin-1-yl	F	H	H	CH_3	MH^+ 421
55	4-methyl-piperazin-1-yl	F	H	H	CH_2-CH_3	MH^+ 435
56	4-methyl-piperazin-1-yl	F	CH_2-CH_3	H	CH_3	MH^+ 449
57	4-methyl-piperazin-1-yl	F	CH_2-CH_3	H	H	MH^+ 435

And

In examples 58 to 64 R is of formula (d)

Example	R_8	R_a	M.S. Data
58	3-*S*-methyl-piperazin-1-yl	CH_3	MH^+ 452
59	3-*R*-methyl-piperazin-1-yl	H	MH^+ 438
60	3-*R*-methyl-piperazin-1-yl	CH_3	MH^+ 452
61	4-benzyl-1-piperazinyl	H	MH^+ 514
62	4-benzyl-1-piperazinyl	CH_3	MH^+ 528
63	1-piperazinyl	CH_3	MH^+ 438
64	1-piperazinyl	H	MH^+ 424

And

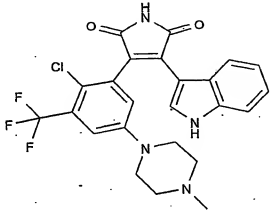
In examples 65 to 88 R is of formula (e)

Example	R_9	R_a	R_b	M.S. Data
65	-(4,7-diaza-spiro[2.5]oct-7-yl)	H	CH_3	MH^+ 464
66	-(4,7-diaza-spiro[2.5]oct-7-yl)	CH_3	H	MH^+ 465
67	3-ethyl-piperazin-1-yl	CH_3	H	MH^+ 467
68	-(4,7-diaza-spiro[2.5]oct-7-yl)	H	H	MH^+ 451
69	3-ethyl-1-piperazinyl	H	H	MH^+ 453
70	3-*R*-methyl-piperazin-1-yl	CH_3	H	MH^+ 453
71	3-*R*-methyl-piperazin-1-yl	H	H	MH^+ 439
72	3-*S*-methyl-piperazin-1-yl	CH_3	H	MH^+ 453
73	3-*S*-methyl-piperazin-1-yl	H	H	MH^+ 439
74	4-methyl-3-*S*-methyl-piperazin-1-yl	CH_3	H	MH^+ 467
75	4-methyl-3-*S*-methyl-piperazin-1-yl	H	H	MH^+ 453
76	4,7-diaza-spiro [2.5] oct-7-yl	CH_3	H	MH^+ 464

77	4,7-diaza-spiro [2.5] oct-7-yl	H	F	MH^+ 479
78	4,7-diaza-spiro [2.5] oct-7-yl	CH_2-CH_3	H	MH^+ 479
79	4,7-diaza-spiro [2.5] oct-7-yl	H	$CH(CH_3)_2$	MH^+ 495
80	4,7-diaza-spiro [2.5] oct-7-yl	H	OCH_3	MH^+ 471
81	4,7-diaza-spiro [2.5] oct-7-yl	CH_3	CH_2-CH_3	MH^+ 451
82	4,7-diaza-spiro [2.5] oct-7-yl	H	CH_2-CH_3	MH^+ 465
83	4,7-diaza-spiro [2.5] oct-7-yl	$CH(CH_3)_2$	H	MH^+ 451
84	4,7-diaza-spiro [2.5] oct-7-yl	CH_3	CH_3	MH^+ 479
85	4,7-diaza-spiro [2.5] oct-7-yl	CH_3	Cl	MH^+ 499
86	4,7-diaza-spiro [2.5] oct-7-yl	H	Cl	MH^+ 485
87	4,7-diaza-spiro [2.5] oct-7-yl	CH_2-CH_3	CH_3	MH^+ 492
88	3-ethyl-piperazin-1-yl	CH_2-CH_3	CH_2-CH_3	MH^+ 494

* The compound of Example 76 is converted into its bis-trifluoroacetate or acetate salt.

or most preferably COMPOUND is 3-[2-Chloro-5-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione having the formula I



(I)

Even more preferred, Compound means any of the other definitions of COMPOUND wherein the compound has an activity on PKC alpha, PKC beta, PKC gamma, PKC epsilon, PKC theta, or on a combination of these enzymes.

Compounds of formula I and methods for the preparation of such compounds are in particular generically and specifically disclosed in the patents and patent application WO2003082859, in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims is hereby incorporated into the present application by reference to this publication.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

Alkyl or alkoxy may be straight or branched. Phenyl-C_{1-4}alkyl is preferably benzyl or phenethyl. In C_{1-4}alkoxy-C_{1-4}alkyl the alkoxy moiety is preferably methoxy or ethoxy and the alkyl moiety preferably methyl or ethyl; a suitable example is e.g. 2-methoxyethyl. Halogen may be F, Cl, Br or I, preferably F, Cl or Br. Halogeno–C_{1-4}alkyl is alkyl wherein one or more H are replaced by halogen, e.g. Cl or F, e.g. CH_2Cl, CH_2F or CF_3

R is preferably a radical of formula (a), (c) or (e).

In the radical of formula (a) or (c), R_2 or R_{15} is preferably in para to R_1 or R_{14}, respectively. R_3 is preferably in meta to R_1. In the radical or formula (e), R_9 is preferably 4,7-diaza-spiro [2.5] oct-7-yl.

PKC is protein kinase C

CDK is cyclin dependent kinase

PKA is protein kinase A

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethylpiperazine.

When a basic group and an acid group are present in the same molecule, a compound of formula I may also form internal salts.

The invention further relates to the use of COMPOUND or a N-Oxide or a pharmaceutically acceptable salt thereof for the manufacture of medicament having an activity on protein kinases PKC alpha, PKC beta, PKC gamma, PKC epsilon, PKC theta, CDK-1, KDR, PKA, Flt-1, Flt-2, Flt-3 or Flt-4, or on a combination of the above enzymes, for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain

inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

The invention also relates to a combination of COMPOUND or a pharmaceutically acceptable salt thereof with one or more drugs used for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis to treat warm-blooded animals including mammals, especially humans.

It has now surprisingly been demonstrated that neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis can be successfully treated with COMPOUND or pharmaceutically acceptable salt thereof.

The invention thus relates to the use of COMPOUND , to treat neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

Depending on species, age, individual condition, mode of administration, and the clinical picture in question, effective doses, for example daily doses of about 10-1000 mg, preferably 10-50 mg or 50-200mg or 200-400mg, especially 50-100mg or 300-400 mg, are administered to warm-blooded animals of about 70 kg bodyweight. For adult patients with neurological and vascular disorders related to beta-amyloid generation and/or aggregation, especially neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

The invention relates likewise to a process or a method for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation, especially neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis. The COMPOUNDS thereof can be administered as such or especially in the form of pharmaceutical compositions, prophylactically or therapeutically, preferably in an amount effective against the said diseases, to a warm-blooded animal, for example a human, requiring such treatment. In the case of an individual having a bodyweight of about 70 kg the daily dose administered is from approximately 0.01 g to approximately 5 g, preferably from approximately 0.25 g to approximately 1.5 g, more preferably 0.01g to 0.05g, even more preferably 0.025g to 0.1g most preferably 0.05g to 1g of a compound of the present invention.

The invention relates also to a method for administering to a human subject suffering from a neurological and vascular disorders related to beta-amyloid generation and/or aggregation, especially neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis, COMPOUND or a pharmaceutically acceptable salt thereof, which comprises administering a pharmaceutically effective amount of COMPOUND or a pharmaceutically acceptable salt thereof to the human subject, preferably once daily for a period exceeding 3 months. The invention relates especially to such method wherein a daily dose of 200 to 800 mg, or 10mg to 200mg especially 400-600 mg or 10–100mg, preferably 400 mg or 10-50mg, of salt is administered.

The invention also relates in a combination which comprises (a) COMPOUND or a pharmaceutically acceptable salt thereof and (b) a therapeutic agent for the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation, most preferably a combination wherein the combination partners are present in synergistically effective amounts.

Surprisingly, it has been found a synergistic effect of a combination as defined herein has greater efficacy than the effects that can be achieved with either type of combination partner

alone, i.e. greater than the effects of a monotherapy using only one of the combination partners as defined herein.

The effective dosage of each of the combination partners employed in the combination may vary depending on a variety of factors including the particular combination of the pharmaceutical compound partners, the route of administration, the severity of the disease, the renal and hepatic functions of the patient. The molar ratio (a)/(b) of the combination partners is about 0.1 to 10, most preferably 0.3 to 3 and the unit dosage form contains 20 to 200 mg, most preferably 50 to 150 mg of 3-[2-Chloro-5-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione of the formula I.

Example 89:

Cell culture

HEK/APPswe cells are plated in microtiter plates precoated with 10 µg/ml poly-D-lysine at 12'000 cells/well in 100 µl/well DMEM medium supplemented with 10% FCS, 0.25 mg/ml G418 sulfate, 1% penicillin streptomycin. The following day, supernatant is replaced with 90 µl/well of fresh medium and 10 µl/well of compound diluted in culture medium are added. Two types of control wells are used: cell culture medium without cells plus 10 µl/well of all compound dilutions (background signals) and cell culture medium from untreated cells (positive control). 24 hours later after compound addition, conditioned medium is collected and Aβ levels determined by a specific sandwich ELISA.

$A\beta_{40}$ and $A\beta_{42}$ detection by sandwich ELISA

For the sandwich ELISA, the maxisorp microtiterplates are coated overnight at 4°C with 100 µl/well of the monoclonal antibody 25H10 diluted 1:1000 in PB for $A\beta_{40}$ detection or monoclonal antibody B10E7 diluted 1:2750 for detection of $A\beta_{42}$. Wells are then emptied, washed three times with 350 µl PBS and blocking is performed for 2 hours at room temperature with 200 µl/well of 2 % BSA, 0.05% Tween20 in PBS. After washing the wells as described above, 10 µl of the conditioned media samples to be tested are added to wells containing 90 µl of medium and 0.18 µg/ml of biotinylated monoclonal β1 antibody and incubated overnight at 4°C. Wells were washed as described above and 100 µl/well of alkaline phosphatase coupled to streptavidin diluted 1:5'000 in medium are added. After 1 hour incubation at room temperature wells are washed as described above and alkaline phosphatase activity is determined by adding 100 µl/well of diethanolamine buffer, pH 9.8

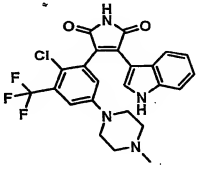
(100 mM diethanolamine, 1 mM $MgCl_2$, pH adjusted to 9.8 with 2 M HCl) containing the chemiluminescent CSPD substrate (25 mM stock solution diluted 1:416) and the enhancer Emerald II (diluted 1:10). After 15 minutes incubation at room temperature in the dark, plates are measured on the luminometer (Analyst AD; LJL Biosystems, USA $A\beta_{40}$). Values are given as % reduction of Aβ. The 100% reduction value is calculated from a series of wells containing only medium and extract and the 0% reduction value from conditioned medium only. Samples are measured in triplicate. A reference compound is included in all plates as control for assay performance.

MTS assay

To determine cytotoxicity, cells are tested by the MTS colorimetric kit performed essentially according to the manufacturer's specifications (Promega, #G5430X). After collecting the conditioned medium for the sandwich ELISA, the rest of the conditioned medium is removed completely and replaced with 100 µl/well culture medium containing one fifth of MTS solution prepared as recommended in the kit. After 3 hours incubation at 37°C, absorbance is read at an OD of 490 nm with a reference wavelength set to 630 nm. Values are given as % metabolic rate (n=6). The 0% value is calculated from wells which had no cells, 100% from wells with an untreated cell layer

Example 90:

3-[2-Chloro-5-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione



This compound has the following activities in cell-free enzyme assays:

PKC alpha	21 nM

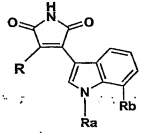
PKC beta	30 nM
PKC gamma	< 500 nM
PKC epsilon	514 nM
PKC theta	186 nM
CDK-1	< 10 microM
KDR	< 10 microM
PKA	< 10 microM
Flt-1	< 10 microM
Flt-2	< 10 microM
Flt-3	< 10 microM
Flt-4	< 10 microM

The compound of Example 90 demonstrates a clear reduction of Abeta secretion in the medium of HEK/APPswe cell cultures at concentrations below 1 microM, without having any effect on cellular viability.

Claims:

1. Use of a an inhibitor of one or more of protein kinases PKC alpha, PKC beta, PKC gamma, PKC epsilon, PKC theta, CDK-1, KDR, PKA, Flt-1, Flt-2, Flt-3 and Flt-4, for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

2. The use according to claim 1 wherein the inhibitor is a compound of formula I



I

wherein

Ra is H; CH3; CH2-CH3; or isopropyl,

Rb is H; halogen; C1-6alkoxy; or C1-6alkyl, and either

I. R is a radical of formula (a)

(a)

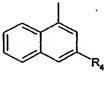
wherein

R1 is piperazin-1-yl optionally substituted by CH3 in position 3 or 4; or 4,7-diaza-spiro [2.5] oct-7-yl;

R2 is Cl; Br; CF3; or CH3; and

R3 is H; CH3; or CF3; R3 being other than H when Ra is H or CH3, Rb is H and R1 is 4-methyl-1-piperazinyl; or

II. R is a radical of formula (b)



(b)

wherein

R4 is piperazin-1-yl substituted in positions 3 and/or 4 by CH3; or 4,7-diaza-spiro [2.5] oct-7-yl; Ra being other than H or CH3 when R4 is 4-methyl-1-piperazinyl; or

III. R is a residue of formula (c)

(c)

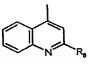
wherein

R14 is piperazin-1-yl optionally substituted by CH3 in position 3 and/or 4 or in position 3 by ethyl, phenyl-C1-4alkyl, C1-4alkoxy-C1-4alkyl or halogeno–C1-4alkyl; or 4,7-diaza-spiro [2.5] oct-7-yl;

R15 is halogen; CF3; or CH3; R15 being other than CH3 when Ra is H or CH3, Rb is H and R14 is 4-methyl-1-piperazinyl; and

R16 is H; CH3; or CF3; R16 being other than H when R15 is Cl, Ra is H or CH3, Rb is H and R14 is 4-methyl-1-piperazinyl; or

IV. R is a radical of formula (d)

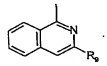


, (d)

wherein R8 is piperazin-1-yl, 3-methyl-piperazin-1-yl or 4-benzyl-piperazin-1-yl;

or

V. R is a radical of formula (e)



(e)

wherein R9 is 4,7-diaza-spiro [2.5] oct-7-yl; or piperazin-1-yl substituted in position 3 by methyl or ethyl and optionally in position 4 by methyl;

or a pharmaceutically acceptable salt thereof.

3. Use according to claim 1 or 2 wherein the inhibitor is a compound selected from any one of the examples 1 to 88;

or a pharmaceutically acceptable salt thereof.

4. Use according to claim 1, 2 or 3 wherein the inhibitor is 3-[2-Chloro-5-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione;

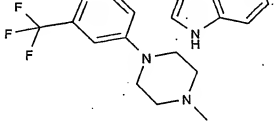
or a pharmaceutically acceptable salt thereof.

5. Use according to any one of the claims 1-4 wherein a daily dose of 10 to 800 mg of a compound is administered to an adult human.

6. Use according to any one of claims 1 – 5 wherein the disorder to be treated is selected from Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

7. Use according to any one of claims 1 – 5 wherein the disorder to be treated is Alzheimer's disease.

8. A method of treating mammals suffering from neurological and vascular disorders related to beta-amyloid generation and/or aggregation which comprises administering to a said mammal in need of such treatment a pharmaceutical composition comprising
(a) a dose, effective against neurological and vascular disorders related to beta-amyloid generation and/or aggregation, of 3-[2-Chloro-5-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione having the formula I



(I)

or a pharmaceutically acceptable salt thereof and

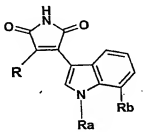
(b) a therapeutically effective amount of a second drug selected from drugs used to treat neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

9. A combination according to claim 8 wherein the combination partners are present in synergistically effective amounts.

10. Use of an inhibitor according to any one of claims 1 - 4 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

11. Use of an inhibitor according to any one of claims 1 - 4 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of Alzheimer's disease.

12. A commercial package comprising an inhibitor of formula I



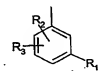
I

wherein

Ra is H; CH3; CH2-CH3; or isopropyl,

Rb is H; halogen; C1-6alkoxy; or C1-6alkyl, and either

I. R is a radical of formula (a)



(a)

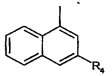
wherein

R1 is piperazin-1-yl optionally substituted by CH3 in position 3 or 4; or 4,7-diaza-spiro [2.5] oct-7-yl;

R2 is Cl; Br; CF3; or CH3; and

R3 is H; CH3; or CF3; R3 being other than H when Ra is H or CH3, Rb is H and R1 is 4-methyl-1-piperazinyl; or

II. R is a radical of formula (b)



(b)

wherein

R4 is piperazin-1-yl substituted in positions 3 and/or 4 by CH3; or 4,7-diaza-spiro [2.5] oct-7-yl; Ra being other than H or CH3 when R4 is 4-methyl-1-piperazinyl; or

III. R is a residue of formula (c)

(c)

wherein

R14 is piperazin-1-yl optionally substituted by CH3 in position 3 and/or 4 or in position 3 by ethyl, phenyl-C1-4alkyl, C1-4alkoxy-C1-4alkyl or halogeno–C1-4alkyl; or 4,7-diaza-spiro [2.5] oct-7-yl;

R15 is halogen; CF3; or CH3; R15 being other than CH3 when Ra is H or CH3, Rb is H and R14 is 4-methyl-1-piperazinyl; and

R16 is H; CH3; or CF3; R16 being other than H when R15 is Cl, Ra is H or CH3, Rb is H and R14 is 4-methyl-1-piperazinyl; or

IV. R is a radical of formula (d)

(d)

wherein R8 is piperazin-1-yl, 3-methyl-piperazin-1-yl or 4-benzyl-piperazin-1-yl; or

V. R is a radical of formula (e)

(e)

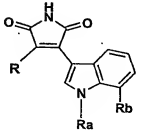
wherein R9 is 4,7-diaza-spiro [2.5] oct-7-yl; or piperazin-1-yl substituted in position 3 by methyl or ethyl and optionally in position 4 by methyl;

or a pharmaceutically acceptable salt thereof in the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation,

together with instructions for simultaneous, separate or sequential use thereof in the treatment of a proliferative disease.

Abstract

The invention relates to the use of an inhibitor of formula I



I

(I)

or a pharmaceutically acceptable salt thereof having an activity on protein kinases PKC alpha, PKC beta, PKC gamma, PKC epsilon, PKC theta, CDK-1, KDR, PKA, Flt-1, Flt-2, Flt-3 or Flt-4, or on a combination of the above enzymes, for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation such as neurodegenerative diseases like Alzheimer's disease, Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis